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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application of:	Doyle et al.	Confirmation No.:	8182
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For:	Promoting Whole Body Health	Attorney Docket No:	11537-004-999

DECLARATION OF DR. STEVEN OFFENBACHER UNDER 37 C.F.R. §1.132

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

I, Dr. Steven Offenbacher, D.D.S., Ph.D., M.MSc. do declare and state that:

1. I am presently Professor of Periodontology at the University of North Carolina, Chapel Hill, North Carolina, holding the titles of Distinguished Professor and Director of the Center for Oral and Systemic Diseases at the School of Dentistry. I have over 25 years of experience in the field of Periodontal Medicine and Molecular Epidemiology, and have published over 120 research papers in this area. My research focuses on the role of inflammatory mediators in periodontal diseases, with a particular interest in the connection between oral health and systemic conditions. My academic and technical experience and honors, and a list of my publications, are set forth in my curriculum vitae, attached hereto as Appendix 1.

2. I was asked to perform experiments to evaluate the efficacy of treating the oral cavity with antimicrobial agents on promoting whole body health. The following experiments were designed in collaboration with Robert E. Singer, a co-inventor of the above-captioned application, and were performed by me or under my supervision.

3. We developed an animal model for periodontal infection-induced atherosclerosis in order to determine the efficacy of treatment. Atherosclerosis was chosen as a prototypic human systemic disease to test the effect of oral hygiene on whole body health. The model used heterozygous ApoE knockout mice, which are pro-atherogenic without being placed on a high-fat diet. Chronic localized infections with periodontal organisms were induced in these mice. The infection was then treated with local or systemic administration of the following antimicrobials: amoxicillin, cetylpyridinium chloride (CPC), stannous fluoride (SF), or zinc citrate. Left untreated, these localized infections induce systemic inflammatory responses and aortic atheroma lesions in the animals.

4. Parameters evaluated included mouse weight as a marker of overall general health. The mice were also tested by assaying for serum levels of amyloid A (SAA). SAA is the mouse equivalent of C reactive protein (CRP), the hepatic acute phase inflammatory response marker currently used as predictive of atherosclerosis. We determined that SAA is highly correlated with the degree of aortic atherogenesis in this model. Thus, the measure of SAA represents not only a good marker of the systemic inflammatory response due to the infection in this model, but also reflects the aortic lesion formation. Inhibition of development of lesions was confirmed by post-mortem analysis of mice.

5. From these studies, I conclude that the antimicrobials tested are effective at reducing the systemic inflammatory response to localized periodontal infection in this mouse model. The data demonstrate the beneficial effect of treatment of the oral infection with antimicrobials on whole body health. Details of the experiments and results are presented in paragraphs 6 – 12, below.

6. The Mouse Model Three breeding colonies were established in our facility, including a wild-type C57Bl/6J colony, an ApoE knock-out colony, and a heterozygous colony using ApoE-/- males and wild-type C57Bl/6J (ApoE+/+) females. Experimental mice were generated in house from the progeny of the three breeding colonies. Pups were weaned at 3-4 weeks of age and randomly assigned to experimental groups. Open cylindrical chambers (titanium wire shaped in cylindrical open coils, 1cm long, 0.5 cm diameter) were surgically inserted subcutaneously in the flank of the mice at 6 weeks of age and left to heal for two weeks

after surgery. The subcutaneous chamber represents a closed compartment into which the injection of bacteria can create a localized infection. In order to ensure the infection remained localized and to emulate a chronic human infection, mice were immunized with intra-chamber injection of either buffer (control mice) or 10^9 CFU of heat-killed *P.gingivalis* (*Pg*) strain A7436 (infected mice) followed by a three-week period to allow for the development of a protective immune response. This time period has been shown in previous experiments to permit a robust bacterial-specific IgG response in this model. Mice were then challenged by intra-chamber injection of either buffer or 10^8CFU of live *P.gingivalis*, and again three weeks later. Mice were sacrificed three weeks after the second challenge.

7. This model mimics a chronic-type of inflammatory response to a localized infection similar to that observed in most forms of human periodontal diseases. Parameters evaluated in this model include:

- mouse weight as a marker of overall general health,
- inflammatory and acute phase response (serum levels of IL-6 and SAA, measured using commercial ELISA kits), and
- aorta atheroma lesion size (histomorphometric analysis of frozen sections or en face morphometric analysis of stereomicroscopic images of stained aortic tree).

8. Animal Treatment Protocol The overall generalized animal protocol was followed as described under #6 above. Treatment with test compounds or saline, injected daily either intra-peritoneally or intra-chamber, started two (2) days before live *Pg* challenge and continued for thirty (30) days after. Mice were bled the day prior to immunization, the day before treatment start, and every week following injection of live bacteria (days 4, 11, 18, 25, and 32 following live *Pg* challenge). Mice were sacrificed at day 32 following injection of live *Pg*.

9. In a first experiment, various dosages of amoxicillin, stannous fluoride, and zinc citrate were tested, using the experimental timeline shown below in Figure 1. Drug treatments had no significant effect on weight gain as compared to saline controls. The effect of treatment on average weight and SAA concentration is shown below in Figure2. Repeated ANOVA showed that all 3 drugs, at all concentrations, significantly suppressed the increase in SAA seen at day 5 and day 10 at $P<0.05$.

Experimental Timeline

Figure 1

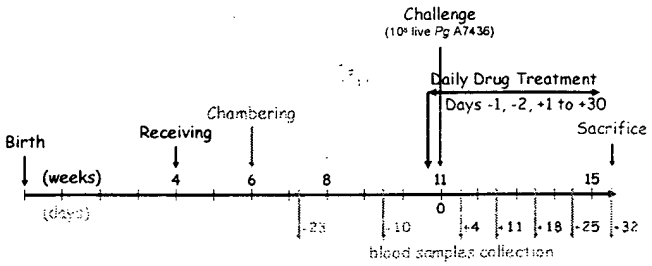
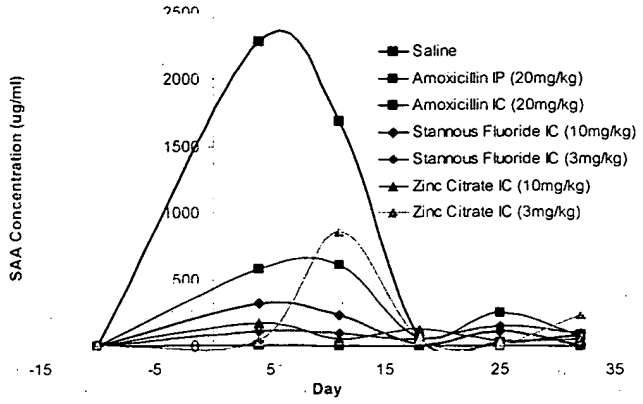


Figure 2: Kinetic response of mean SAA concentration for each mouse treatment group measured at different days before and after live bacterial challenge (mean per group in micrograms/ml).



10. In the next set of experiments, cetylpyridinium chloride (CPC), in addition to lower doses of stannous fluoride and zinc citrate were tested in the animal model. The overall animal protocol was similar to the one described for the experiment described above, with the exceptions of ending treatment 9 days after live *Pg* challenge, and sacrificing the mice 11 days after live *Pg* challenge, according to the following experimental timeline shown in Figure 3. The effect of treatment on SAA concentration is shown in Figures 4 below. Repeated ANOVA shows that all dosages of stannous fluoride and CPC significantly inhibited the acute phase response.

Experimental Timeline

Figure 3

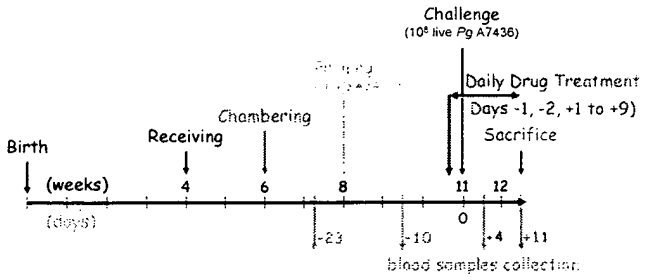
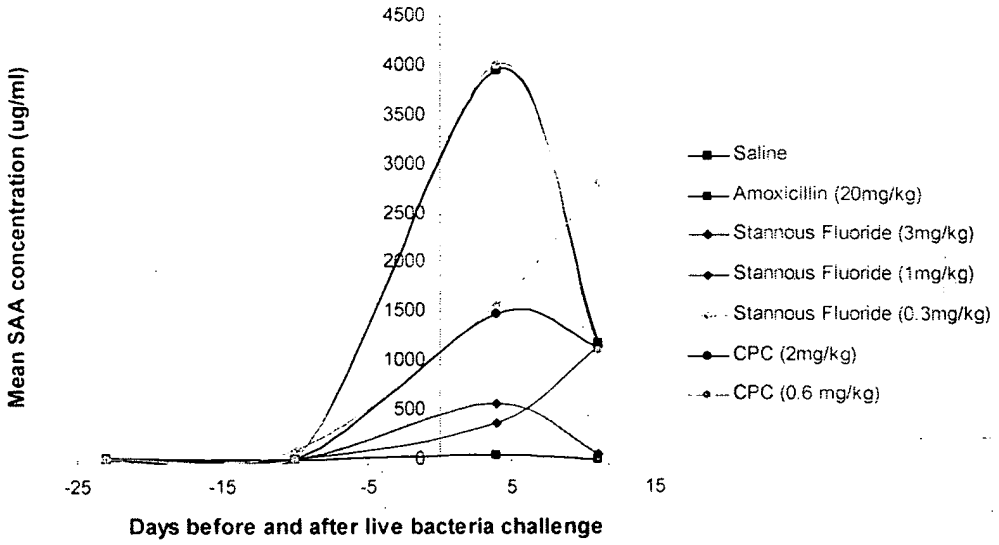


Figure 4: Kinetic response of mean SAA concentration for each mouse treatment group measured at different days before and after live bacterial challenge (mean per group in micrograms/ml).



11. In the following set of experiments, additional dosages of CPC were tested. The overall animal protocol, treatment and live *Pg* challenge were as described above, according to the following experimental timeline in Figure 5. The effect of treatment on SAA concentration is shown in Figure 6 below and again indicated a significant dose-dependent suppression of SAA.

Experimental Timeline

Figure 5

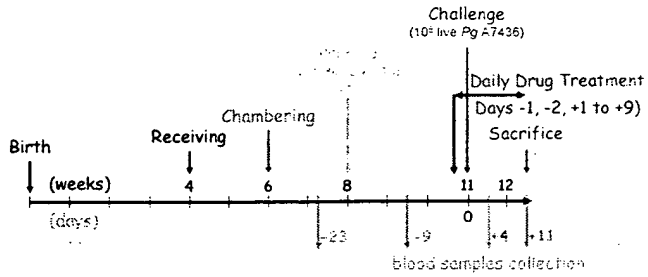
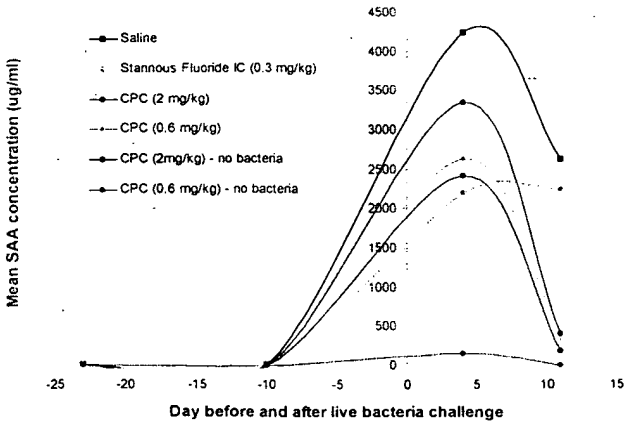


Figure 6: Kinetic response of mean SAA concentration for each mouse treatment group measured at different days before and after live bacterial challenge (mean per group in micrograms/ml).



12. Conclusions The above studies demonstrate the use of a murine model to test the effect of treating the oral cavity with antimicrobial agents on the immune system and promoting whole body health. In this model, untreated animals develop periodontal infection-induced serum inflammatory responses and aortic lesions. Our findings indicate that effective dosages of stannous fluoride, zinc citrate, and CPC inhibited periodontal infection-induced systemic inflammatory response. Furthermore, there were clear dose-dependent effects on SAA inhibition with stannous fluoride, zinc citrate and CPC. Moreover, the body weights of the treated animals increased regularly during the course of the experiments. These results indicate that the treatments with the test compounds protected the mice from the adverse consequences of periodontal infection on whole body health. Taken together, these studies demonstrate that treatment of the oral cavity with antimicrobial agents can reduce systemic inflammatory response, a response which has been shown to be associated with an inhibition of aorta atherosclerotic lesions, and to promote whole body health in this model. The dose-dependent action of these agents are consistent with a direct effect on these drugs on the infection induced inflammatory systemic response.

13. I hereby declare further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true and further that I make these statements with the knowledge that willful false statements and the like are punishable by fine or imprisonment, or both, under § 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Date: 1/3/05

Steven Offenbacher, D.D.S., Ph.D., M.MSc.

Steven Offenbacher, D.D.S.,Ph.D.,M.MSc.
Summary Curriculum Vitae

Distinguished Professor and Director of the Center for Oral and Systemic Diseases at the School of Dentistry at the University of North Carolina, Dr. Offenbacher joined the department of Periodontology at UNC in 1991 and was awarded full professor status in 1994. He has earned many national and international distinctions including the Basic Research in Periodontal Disease Award from the International Association for Dental Research. He is the first dental scientist to be awarded the prestigious national Healthy Mothers, Healthy Babies Special Impact Award. Most recently, he was appointed as the UNC School of Dentistry's first OraPharma Distinguished Professor of Periodontal Medicine.

Dr. Offenbacher participates in numerous university, state and national committees and is recognized as an international expert and lecturer on periodontology and systemic diseases. He is former President of the American Association of Dental Research (AADR) and serves on the editorial board of three dental journals. He teaches and acts as a primary mentor for advanced students and visiting scientists. Additionally, Dr. Offenbacher continues in the care and treatment of patients (10-20% effort) as a periodontist in the Dental Faculty Practice at UNC.

His years of examining the role of inflammatory mediators in periodontal diseases have produced new and important findings between oral health and systemic conditions thereby establishing the field of Periodontal Medicine. He has published over 120 documents (papers, articles, book chapters, manuscripts), written over 150 abstracts and is credited with 6 patents. Additionally, his laboratory has gained international recognition and stature.

His research focuses on the following areas:

- Molecular epidemiology to investigate the relationship of periodontal disease to premature birth, atherosclerosis, heart disease and diabetes
- Clinical and translational research in pharmacological modification of the host response to treat periodontal diseases
- Periodontal clinical trials to improve cardiovascular and diabetic health and pregnancy outcomes.

Prior to joining the academic staff at UNC, Dr. Offenbacher was a member of the faculty at Emory University from 1981-1990 and served as chairman of the department of periodontology from 1982-1985.

Education:

Institution	Degree	Date	Degree Major
Harvard Medical School	M.MSc.	1980	Oral Biology
Harvard School of Dental Medicine	Certificate	1980	Periodontology and Oral Medicine
Forsyth Dental Center	Post-doc	1980	Pharmacology
Virginia Commonwealth University	Ph.D.	1977	Biochemistry
Virginia Commonwealth University	D.D.S.	1976	Dentistry
Boston University	B.A.	1972	Chemistry

C. Research Support.

NIH/NIDCR U01 DEO14577 (Offenbacher PI) 06/01/03-05/31/08
MOTOR: Maternal Oral Therapy to Reduce Obstetric Risk -A 5-year multi-centered clinical trial to evaluate the effects of periodontal therapy on preterm birth.

NIDCR 1 P60-DE 13079 (Flood PI.) 05/01/99-07/31/05
Comprehensive Center for Inflammatory Disorders
Project 13 Oral Microbes and Cardiovascular Disease (Offenbacher PI)
To conduct studies as part of a Comprehensive Research Center on Oral Health focusing on the role of inflammation in oral and systemic health.

NIDCR U01 DE 13940 (Genco, PI, Offenbacher Co-PI, Beck Co-PI) 01/01/01-05/31/05
Periodontal Intervention for Cardiac Events: Pilot Trial - This is a pilot study to test whether a periodontal disease intervention reduces cardiac events in individuals who have already had an event.

NIDCR U01 DE 13940 (Genco, Offenbacher Co-PI) 06/01/01 – 05/31/05
Periodontal Program to Prevent Cardiovascular Events - One of five field centers as a subcontract to the State University of New York at Buffalo which will recruit patients, provide periodontal treatment, and monitor cardiovascular outcomes for this study.

NIDCR R21 DE14984 (Offenbacher PI) 09/30/02-09/29/05
Periodontal Disease in Diabetic Women with Preterm Birth - This is a collaborative study between the periodontal and molecular epidemiology expertise at the UNC School of Dentistry and the OB/GYN expertise at the University of Hawaii School of Medicine that examines the role of periodontal disease in preterm deliveries among pregnant diabetic Asian & Pacific Islander (API) women.

NIH/CRR (Orringer PI) 05/1/03-04/30/08
General Clinical Research Center Supplement - A supplement to the GCRC to add the GO-Health Center in the School of Dentistry as a component of the GCRC.

AAOMS Foundation (White PI) 01/15/98-01/14/05
Morbidity/Social/Economic Cost of Retaining Third Molars - This study involves GCF analysis of PGE_2 and IL-1β as predictors of 3rd molar morbidity in a prospective clinical trial.

Procter & Gamble (Offenbacher PI) 05/01/00-6/31/05

Effects of Periodontal Therapy on Markers of Acute Phase Response (APR), Oxidative Stress and Impaired Glucose Metabolism - The overall purpose of the proposal is to assess the effects of periodontal disease interventions on the hepatic acute phase response, markers of systemic oxidative stress and insulin/glucose tolerance.

Proctor & Gamble (Offenbacher PI) 1/3/05 – 12/30/05
Identification of Candidate Predictor Biomarkers Associated with Experimental Gingivitis Response in Humans- This study works towards identifying individuals at risk for developing periodontal inflammation by collecting and analysing information on predictor biomarkers.

Johnson & Johnson (Offenbacher PI) 1/3/04 – 12/30/04
Murine *P. Gingivalis* Infection Model for Evaluating the Efficacy of Anti-Periodontitis Agents - The aim of this study is to identify potential new drugs for the treatment of periodontal disease and to determine their influence on the progression of the disease.

OraPharma, Inc (Offenbacher PI) 07/09/00-12/31/04
Development of a Second Generation Therapeutic - This project seeks to develop a combination drug or single agent drug formulation in a biodegradable, controlled drug delivery system for subgingival delivery to treat periodontal disease.

Principal Investigator/Program Director (Last, first, middle): Offenbacher, Steven

BIOGRAPHICAL SKETCH

Provide the following information for the key personnel in the order listed for Form Page 2.
Follow the sample format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME	POSITION TITLE
Offenbacher, Steven	Professor

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	YEAR(s)	FIELD OF STUDY
Boston University, Boston, MA	BA	1972	Chemistry
Virginia Commonwealth University, Richmond	DDS	1976	Dentistry
Virginia Commonwealth University, Richmond	PhD	1977	Biochemistry
Harvard Medical School, Boston, MA	MMSc	1980	Oral Biology
Harvard School of Dental Medicine, Boston, MA	Certificate	1980	Periodontology

A. Positions and Honors.

Positions and Employment

1976-1977 Instructor, Department of Biochemistry, Medical College of Virginia, Richmond, VA
1977-1980 Research Fellow in Periodontology, Harvard School of Dental Medicine, Boston, MA
1980-1987 Assistant Professor of Periodontology and Oral Biology, Emory University School of Dentistry
1980-1991 Assistant /Associate Professor of Biochemistry, Emory University School of Medicine
1981-1985 Chairman, Department of Periodontology, Emory University School of Dentistry
1984-1991 Guest Researcher, Anaerobic Microbiology Laboratory, Centers for Disease Control
1984-1991 Guest Researcher, Yerkes Primate Center, Emory University, Atlanta, Georgia
1987-1991 Associate Professor of Periodontology and Oral Biology/ Emory University School of Dentistry
1988-1991 Associate Professor in the Winship Cancer Center, Emory University School of Medicine
1991-1994 Associate Professor of Periodontology, University of North Carolina at Chapel Hill
1994-Present Professor of Periodontology, University of North Carolina at Chapel Hill
1998-Present Director, Center for Oral and Systemic Diseases

Honors

1975 Johnson and Johnson Dental Research Award
1976 Procter & Gamble Research Award
1977 Virginia Academy of Science, First Prize
1999 IADR Basic Science Award in Periodontology
1999 William J. Gies Foundation Award
2000 Healthy Mothers, Healthy Babies Coalition Special Impact Award
2003 OraPharma Distinguished Professor of Periodontal Medicine
2004 Clinical Research Award, AAP, Maternal periodontal disease is associated with an increased risk for preeclampsia. *Obstet Gynecol.* 2003;101(2):227-31.

B. Selected peer-reviewed publications (in chronological order).

1. Offenbacher S, Williams RC, Jeffcoat MK, Howell TH, Odle BM, Smith MA, Hall CM, Johnson HG and Goldhaber P. Effects of NSAIDs on beagle crevicular fluid cyclooxygenase metabolites and periodontal bone loss. *J Periodontal Res.* 1992;27(3): 207-13.
2. Smith MA, Braswell LD, Boyd DL, Collins JG, Jeffcoat MK, Reddy M, Li KL, Wilensky S, Vogel R, Alfano MC, Offenbacher S. Changes in inflammatory mediators in experimental periodontitis in the Rhesus monkey. *Infect Immunity.* 1993;61(4): 1453-59.
3. Beck JD, Koch GC, Offenbacher S. Attachment loss trends over three years in community-dwelling older adults. *J Periodontol.* 1994;65(8): 737-43.
4. Offenbacher S, Katz V, Fertik G, Collins J, Boyd D, Maynor G, McKaig R, Beck J. Periodontal infection as a possible risk factor for preterm low birth weight. *J Periodontol.* 1996;67(10 Suppl): 1103-13.
5. Offenbacher S, Salvi GE, Beck JD, Williams RC. The design and implementation of trials of host modulation agents. *Ann Periodontol.* 1997; 2(1): 199-212.
6. Beck JD, Sharp T, Koch GG, Offenbacher S. A 5-year study of attachment loss and tooth loss in community-dwelling older adults. *J Periodontol Res.* 1997;32(6): 516-23.
7. Beck JD, Sharp T, Koch GG, Offenbacher S. A study of attachment loss patterns in survivor teeth at 18 months, 36 months, and 5 years in community-dwelling older adults. *J Periodontal Res.* 1997;32(6): 497-505.
8. Slade GD, Offenbacher S, Beck JD, Heiss G, Tyroler HA. Acute-phase Inflammatory Response to Local Periodontal Disease and Systemic Conditions in the US Population. *J Dent Res* 2000;79(1):49-57.
9. Grimm W., Cichon P., van der Hoeven H., Langendijk P.S., Smith F., Worley M.G., Schmitz I., Offenbacher S. The Influence of Sulfate-Reducing Bacteria Colonization of 2 Different Bioresorbable Barrier membranes for GTR. An 18-Month Case-Controlled Microbiologic and Clinical Study. *Int J Periodontics Restorative Dent* 2000;20(1):93-99.
10. Williams R, Offenbacher S. Periodontal medicine: the emergence of a new branch of periodontology. *Periodontol 2000.*2000;23:9-12
11. Page RC, Offenbacher S, Schroeder HE, Seymour GJ and Kornman KS. Advances in the pathogenesis of periodontitis: Summary of developments, clinical implications and future directions. *Periodontol 2000.* 1997;14: 216-48.
12. Offenbacher S, Jared HL, O'Reilly PG, Wells SR, Salvi GE, Lawrence HP, Socransky SS and Beck JD. Potential pathogenic mechanisms of periodontitis associated pregnancy complications. *Ann Periodontol.* 1998;3(1): 233-50.
13. Beck JD, Offenbacher S, Williams R, Gibbs P, and Garcia R. Periodontitis: A risk factor for coronary heart disease? *Ann Periodontol.* 1998;3(1): 127-41.
14. Offenbacher S, Lieff S, Beck JD. Periodontitis-associated pregnancy complications. *Prenat Neonat Med.* 1998;3: 82-85.
15. Elter JR, Beck JD, Slade GD, Offenbacher S. Etiologic models for incident periodontal attachment loss in older adults. *J Clin Periodontol.* 1999:26(2):113-23.
16. Offenbacher S, Salvi GE. Induction of prostaglandin release from macrophages by bacterial endotoxins. *Clin Infect Dis.* 1999;28(3): 505-13.
17. Duncan BB, Schmidt MI, Offenbacher S, Wu KK, Savage PJ, Heiss G. Factor VIII and other hemostasis variables are related to incident diabetes in adults. The Atherosclerosis Risk in Communities (ARIC) Study. *Diabetes Care.* 1999;22(5): 767-72.
18. Schmidt MI, Duncan BB, Sharrett AR, Lindberg G, Savage PJ, Offenbacher S, Azambuja MI, Tracy RP and Heiss G. Markers of inflammation and prediction of diabetes mellitus in adults (Atherosclerosis Risk in Communities Study): A cohort study. *The Lancet.* 1999;353(9165): 1649-52.
19. Kornman KS, Pankow J, Offenbacher S, Beck J, di Giovine F, Duff G. Interleukin-1 genotypes and the association between periodontitis and cardiovascular disease. *J Periodontal Res.* 1999; 34(7): 353-7.
20. Offenbacher S, Madianos PN, Champagne CM, Southerland JH, Paquette DW, Williams RC, Slade G, Beck J. Periodontitis-atherosclerosis syndrome – an expanded model of pathogenesis. *J Periodontal Res.* 1999;34(7): 346-52.
21. McNamara KM, Hall SE, Wilder RS, Lawrence HP, Offenbacher S. Periodontitis and cytokine expression in CD14 deficient patients. *J Int Acad Periodontol.* 1999;1(4): 95-100.
22. Beck JD, Pankow J, Tyroler HA, Offenbacher S. Dental Infections and atherosclerosis. *Am Heart J.* 1999:138(5 Pt 2):S528-33.
23. Paquette DW, Madianos P, Offenbacher S, Beck JD, Williams RC. The concept of "risk" and the emerging discipline of periodontal medicine. *J Contemp Dent Pract.* 1999;1(1):1-8.
24. Slade GD, Offenbacher S, Beck JD, Heiss G, Pankow JS. Acute-phase inflammatory response to periodontal disease in the US Population. *J Dent Res.* 2000;79(1): 49-57.
25. Champagne CM, Madianos PN, Lieff S, Murtha AP, Beck JD, Offenbacher S. Periodontal medicine: emerging concepts in pregnancy outcomes. *J Int Acad* Periodontal. 2000;2(1): 9-13
26. Dasanayake AP, Boyd D, Madianos PN, Offenbacher S, Hills E. The association between porphyromonas gingivalis-specific maternal serum IgG and low birth weight. *J Periodontol.* 2001;72(11): 1491-7.

27. Williams RC, Paquette DW, Offenbacher S, et al. Treatment of periodontitis by local administration of minocycline microspheres: A controlled trial. *J Periodontol.* 2001;72(11): 1535-44.
28. Beck JD, Elter JR, Heiss G, Couper D, Mauriello SM, Offenbacher S. Relationship of periodontal disease to carotid artery intima-media wall thickness: The arteriosclerosis risk in communities (ARIC) study. *Arterioscler Thromb Vasc Biol.* 2001:21(11): 1816-22.
29. Offenbacher S, Lieff S, Boggess K, Murtha AP, Madianos PN, Champagne CM, McKaig RG, Jared HL, Mauriello SM, Auten RL Jr, Herbert WN, Beck JD. Maternal periodontitis and Prematurity: Part 1 – Obstetric outcome of prematurity and growth restriction. *Ann Periodontol.* 2001;6(1): 164-174.
30. Madianos PN, Lieff S, Murtha AP, Boggess KA, Auten RL Jr, Beck JD, Offenbacher S. Maternal periodontitis and prematurity: Part II – Maternal infection and fetal exposure. *Ann Periodontol.* 2001;6(1): 175-82.
31. Beck JD, Offenbacher S. The association between periodontal diseases and cardiovascular diseases: States-of-the-science review. *Ann Periodontal.* 2001;6(1): 9-15
32. Champagne CM, Takebe J, Offenbacher S, and Cooper LF. Macrophage cell lines produce osteoinductive signals that include bone morphogenetic protein-2. *Bone.* 2002;30(1): 26-31.
33. Fabre JE, Goulet JL, Riche E, Nguyen M, Coggins K, Offenbacher S, Koller BH. Transcellular biosynthesis contributes to the production of leukotrienes during inflammatory responses in vivo. *J Clin Invest.* 2002;109(10): 1373-80.
34. Hunt KJ, Pankow JS, Offenbacher S, Kritchevsky SB, Duncan BB, Shahar E, Sharrett AR, Heiss G. B-mode ultrasound-detected carotid artery lesions with and without acoustic shadowing and their association with markers of inflammation and endothelial activation: The atherosclerosis risk in communities study. *Atherosclerosis.* 2002;162(1): 145-55.
35. Genco R, Offenbacher S, Beck J. Periodontal disease and cardiovascular disease: Epidemiology and possible mechanisms. *J Am Dent Assoc.* 2002;133Suppl: 14S-22S
36. Van Dyke TE, Offenbacher S, Braswell L, Lessem J. Enhancing the value of scaling and root-planing: Arestin clinical trial results. *J Int Acad Periodontol.* 2002;4(3): 72-6.
37. Kalachandra S, Lin DM, Offenbacher S. Ethylene-vinyl acetate (EVA) copolymer as a biocompatible intra-oral device for controlled delivery of antimicrobial and antifungal agents. *Current Trends.* 2002;7: 71-84.
38. White RP JR, Offenbacher S, Phillips C, Haug RH, Blakey GH, Marciani RD. Inflammatory mediators and periodontitis in patients with asymptomatic third molars. J Oral Maxillo Surg. 2002; 60(11): 1241-5
39. White RP Jr., Madianos PN, Offenbacher S, Phillips C, Blakey GH, Haug RH, Marciani RD. Microbial complexes detected in the second/third molar region in patients with asymptomatic third molars. *J Oral Maxillofac Surg.* 2002; 60(11): 1234-40
40. Champagne CM, Buchanan W, Reddy MS, Preisser JS, Beck JD, Offenbacher S. Potential for gingival crevice fluid measure as predictors of risk for periodontal diseases. *Periodontal 2000.* 2003;31: 167-80
41. Boggess KA, Lieff S, Murtha AP, Moss K, Beck J, Offenbacher S. Maternal periodontal disease is associated with an increased risk for preeclampsia. *Obstet Gynecol.* 2003;101(2): 227-31.
42. Takebe J, Champagne CM, Offenbacher S, Ishibashi K, Cooper LF. Titanium surface topography alters cells shape and modulates bone morphogenetic protein 2 expression in the J774AAA.1 macrophage cell line. *J Biomed Mater Res A.* 2003;64(2):207-16.
43. Slade GD, Ghezzi EM, Heiss G, Beck JD, Riche E, Offenbacher S. Relationship between periodontal disease and C-reactive protein among adults in the Atherosclerosis Risk in Communities Study. *Arch Intern Med.* 2003;163: 1172-9.
44. Paquette D, Oringer R, Lessem J, Offenbacher S, Genco R, Persson GR, Santucci EA, Willliams RC. Locally delivered minocycline microspheres for the treatment of periodontitis in smokers. *J Clin Periodontal.* 2003;30(9): 787-94
45. Lin D, Smith MA, Champagne C, Elter J, Beck J, Offenbacher S. Porphyromonas gingivalis infection during pregnancy increases maternal tumor necrosis factor alpha, suppresses maternal interleukin-10, and enhances fetal growth restriction and resorption in mice. *Infect Immun.* 2003;71(9): 5156-62.
46. Lin D, Smith MA, Elter J, Champagne C, Downey CL, Beck J, Offenbacher S. Porphyromonas gingivalis infection in pregnant mice is associated with placental dissemination, an increase in the placental TH1/TH2 cytokine ratio, and fetal growth restriction. *Infect Immun.* 2003;71(9): 5163-8.
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C. Research Support.

NIH/NIDCR U01 DEO14577 (Offenbacher PI) 06/01/03-05/31/08
MOTOR: Maternal Oral Therapy to Reduce Obstetric Risk -A 5-year multi-centered clinical trial to evaluate the effects of periodontal therapy on preterm birth.

NIDCR 1 P60-DE 13079 (Flood PI.) 05/01/99-07/31/05
Comprehensive Center for Inflammatory Disorders
Project 13 Oral Microbes and Cardiovascular Disease (Offenbacher PI)
To conduct studies as part of a Comprehensive Research Center on Oral Health focusing on the role of inflammation in oral and systemic health.

NIDCR U01 DE 13940 (Genco, PI, Offenbacher Co-PI, Beck Co-PI) 01/01/01-05/31/05
Periodontal Intervention for Cardiac Events: Pilot Trial - This is a pilot study to test whether a periodontal disease intervention reduces cardiac events in individuals who have already had an event.

NIDCR U01 DE 13940 (Genco, Offenbacher Co-PI) 06/01/01 – 05/31/05
Periodontal Program to Prevent Cardiovascular Events - One of five field centers as a subcontract to the State University of New York at Buffalo which will recruit patients, provide periodontal treatment, and monitor cardiovascular outcomes for this study.

NIDCR R21 DE14984 (Offenbacher PI) 09/30/02-09/29/05
Periodontal Disease in Diabetic Women with Preterm Birth - This is a collaborative study between the periodontal and molecular epidemiology expertise at the UNC School of Dentistry and the OB/GYN expertise at the University of Hawaii School of Medicine that examines the role of periodontal disease in preterm deliveries among pregnant diabetic Asian & Pacific Islander (API) women.

NIH/CRR (Orringer PI) 05/1/03-04/30/08
General Clinical Research Center Supplement - A supplement to the GCRC to add the GO-Health Center in the School of Dentistry as a component of the GCRC.

AAOMS Foundation (White PI) 01/15/98-01/14/05
Morbidity/Social/Economic Cost of Retaining Third Molars - This study involves GCF analysis of PGE_2 and IL-1β as predictors of 3rd molar morbidity in a prospective clinical trial.

Procter & Gamble (Offenbacher PI) 05/01/00-6/31/05

Effects of Periodontal Therapy on Markers of Acute Phase Response (APR), Oxidative Stress and Impaired Glucose Metabolism - The overall purpose of the proposal is to assess the effects of periodontal disease interventions on the hepatic acute phase response, markers of systemic oxidative stress and insulin/glucose tolerance.

Proctor & Gamble (Offenbacher PI) 1/3/05 – 12/30/05
Identification of Candidate Predictor Biomarkers Associated with Experimental Gingivitis Response in Humans- This study works towards identifying individuals at risk for developing periodontal inflammation by collecting and analysing information on predictor biomarkers.

Johnson & Johnson (Offenbacher PI) 1/3/04 – 12/30/04
Murine *P. Gingivalis* Infection Model for Evaluating the Efficacy of Anti-Periodontitis Agents - The aim of this study is to identify potential new drugs for the treatment of periodontal disease and to determine their influence on the progression of the disease.

OraPharma, Inc (Offenbacher PI) 07/09/00-12/31/04
Development of a Second Generation Therapeutic - This project seeks to develop a combination drug or single agent drug formulation in a biodegradable, controlled drug delivery system for subgingival delivery to treat periodontal disease.

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menstrual a., a. of the conceptus computed from the start of the mother's last menstrual period.

mental a. (MA), a measure, expressed in years and months, of a child's measured intelligence relative to age norms as determined by testing with the Stanford-Binet intelligence scale.

physical a., SYN anatomical a.

physiologic a., a. estimated in terms of function.

agen·e·sis (ă-jen'ĕ-sis). Absence, failure of formation, or imperfect development of any part. [G. *a-* priv. + *genesis,* production]

gonadal a., SYN gonadal *aplasia.*

renal a., absence of one or both kidneys, most commonly unilateral with absence of the ipsilateral paramesonephric (müllerian) duct and its derivatives; renal function is normal as long as the remaining kidney is intact; bilateral or complete renal a. is associated with Potter's facies and neonatal death.

thymic a., absence of the thymus, which may be associated with parathyroid a. in DiGeorge syndrome.

agen·i·tal·ism (ă-jen'i-tal-izm). Congenital absence of genitalia.

agen·o·so·mia (ă-gen-ō-sō'mē-ă). Markedly defective formation or absence of the genitalia in a fetus; usually accompanied by protrusion of the abdominal viscera through an incomplete abdominal wall. [G. *a-* priv. + *genos,* sex, + *soma,* body]

agent (ā'jent). **1.** An active force or substance capable of producing an effect. For agents not listed here, see the specific name. **2.** Referring to disease, a factor such as a microorganism, chemical substance, or form of radiation whose presence, excessive presence, or relative absence (as in deficiency diseases) is essential for the occurrence of a disease. [L. *ago,* pres. p. *agens* (*agent-*), to perform]

adrenergic blocking a., a compound that selectively blocks or inhibits responses to sympathetic adrenergic nerve activity (sympatholytic a.) and to epinephrine, norepinephrine, and other adrenergic amines (adrenolytic a.); two distinct classes exist, alpha- and beta-adrenergic receptor blocking a.'s.

α-adrenergic blocking a., an agent that competitively blocks α-adrenergic receptors; used in the treatment of hypertension. SYN alpha-blocker.

β-adrenergic blocking a., a class of drugs that compete with β-adrenergic agonists for available receptor sites; some compete for both β_1 and β_2 receptors (*e.g.,* propranolol) while others are primarily either β_1 (*e.g.,* metoprolol) or β_2 blockers; used in the treatment of a variety of cardiovascular diseases where β-adrenergic blockade is desirable. SYN β-adrenergic receptor blocking a., β-adrenoreceptor antagonist, beta-blocker.

adrenergic neuronal blocking a., a drug that prevents the release of norepinephrine from sympathetic nerve terminals; it does not inhibit the responses of the adrenergic receptors to circulating epinephrine, norepinephrine, and other adrenergic amines.

β-adrenergic receptor blocking a., SYN β-adrenergic blocking a.

alkylating a., a drug or chemical that, via the formation of covalent bonds, forms a derivatized tissue constituent permanently containing part of the drug or chemical compound; frequently carcinogenic and mutagenic.

antianxiety a., a functional category of drugs useful in the treatment of anxiety and able to reduce anxiety at doses which do not cause excessive sedation (*e.g.,* diazepam). SYN anxiolytic (1), minor tranquilizer.

antifoaming a.'s, chemicals that lower surface tension (hence production of foam), used in laboratory evaporations, and also administered with oxygen to relieve the respiratory obstruction aggravated by the foam of edema fluid in pulmonary edema.

antipsychotic a., a functional category of neuroleptic drugs that are helpful in the treatment of psychosis and have a capacity to ameliorate thought disorders (*e.g.,* chlorpromazine, haloperidol). SEE ALSO neuroleptic (3). SYN antipsychotic (1), major tranquilizer.

bacteriostatic a., SYN bacteriostat.

Bittner a., SYN mammary tumor *virus* of mice.

blister a., SYN vesicant.

blocking a., a class of drugs that inhibit (block) a biologic activity or process, such as axonal conduction or transmission ions across a cell membrane; frequently called "blockers."

calcium channel-blocking a., a class of drugs that have ability to inhibit movement of calcium ions across the cell m brane; of particular value in the treatment of cardiovascular orders because of pharmacologic effects such as depressio mechanical contraction of cardiac and smooth muscle and both impulse formation and conduction velocity (*e.g.,* nif pine). SYN calcium antagonist, slow channel-blocking a.

chimpanzee coryza a. (CCA), SYN respiratory syncytial *viru*

cholinergic a., an a. that mimics the action of the parasympati ic nervous system (*e.g.,* methacholine).

contrast a., SYN contrast *medium.*

delta a., SYN hepatitis delta *virus.*

Eaton a., SYN *Mycoplasma pneumoniae.*

embedding a.'s, materials such as celloidin, paraffin, etc. which specimens of tissue are set before being cut into secti for microscopic examination.

enterokinetic a., an a. used to relieve intestinal atony.

F a., SYN F *plasmid.*

fertility a., SYN F *plasmid.*

foamy a.'s, SYN foamy *viruses,* under *virus.*

ganglionic blocking a., an a. that impairs the passage of imp es in autonomic ganglia.

high osmolar contrast a. (HOCA), ionic water-soluble iodi ed contrast media. SYN high osmolar contrast medium.

initiating a., SEE initiation.

inotropic a.'s, drugs that increase the force of contraction cardiac muscle; examples include digitalis glycosides, amrinc and epinephrine.

LDH a., SYN lactate dehydrogenase *virus.*

luting a., a fastening material or cement; *e.g.,* plaster or wa hold casts to an articulator, or material to hold crowns to teet

MS-1 a., a strain of hepatitis A virus.

MS-2 a., a strain of hepatitis B virus.

neuroleptic a., any of a family of drugs producing sedation tranquilization (*e.g.,* chlorpromazine, haloperidol). SEE ALSO a psychotic a. SYN neuroleptic (1).

neuromuscular blocking a.'s, a group of drugs that prev motor nerve endings from exciting skeletal muscle. They either by competing for the neurotransmitter, acetylcholine, (l D-tubocurarine, mivacurium and pancuronium), or by first st ulating the postjunctional muscle membrane and subsequer desensitizing the muscle endplates to the acetylcholine (like s cinylcholine or decamethonium); used in surgery to produce ralysis and facilitate manipulation of muscles.

nondepolarizing neuromuscular blocking a., a compound t paralyzes skeletal muscle primarily by inhibiting transmissior nerve impulses at the neuromuscular junction rather than affecting the membrane potention of motor endplate or mus fibers.

Norwalk a., a strain of epidemic gastroenteritis virus that pears to be related to the calciviruses. [*Norwalk,* Ohio, wh first implicated in disease]

Pittsburgh pneumonia a., SYN *Legionella micdadei.*

promoting a., SEE promotion.

psychotropic a., a chemical compound that influences the man psyche.

reovirus-like a., SYN rotavirus.

sclerosing a., a compound which acts by irritation of the vein intimal epithelium; used in the treatment of varicose veins.

slow channel-blocking a., SYN calcium channel-blocking a.

sympathetic a., SEE sympathomimetic *amine.*

transforming a., SYN mitogen.

TRIC a.'s, strains of *Chlamydia trachomatis* that cause *trac* ma and inclusion conjunctivitis a.'s SEE *Chlamydia trachoma*

Agent Or·ange. An herbicide and defoliant, consisting (2,4,5-trichlorophenoxy)acetic acid, (2,4-dichlorophenoxy)ac acid, and dioxin, that was widely used in the Vietnam War; it been shown to possess residual post-exposure carcinogenic teratogenic properties in humans.

mnemic t., SYN mnemic *hypothesis.*

molecular dissociation t., a t., pertaining to color vision, that gray is the earliest of color sensations, from which are derived, by molecular change, two paired substances that, respectively, detect yellow and blue, and that the yellow gives rise to paired substances for detection of red and green. SYN Ladd-Franklin t.

monophyletic t., SYN monophyletism.

myoelastic t., a t. stating that sound of the human voice is produced by vibrations of the vocal cords resulting from folding upward due to air pressure below, and subsequent movement downward due to elastic tension of cords.

myogenic t., that cardiac movements are due mainly to stimuli originating in the heart muscle itself and that the heart does not act solely in response to nerve stimulation.

Nernst's t., that the passage of an electric current through the tissues causes a dissociation of the ions, with consequent concentration of salts in the solution bathing the cell membranes, the electric stimulus being thereby effected.

neurochronaxic t., t. stating that variations in pitch of the human voice are produced by active muscular contractions synchronized with cycles per second of pitch, no longer believed to be true.

Ollier's t., a t. of compensatory growth; after resection of the articular extremity of a bone, the articular cartilage of the other bone entering into the structure of the joint takes on an increased growth.

omega-oxidation t., that the oxidation of fatty acids commences at the CH_3 group, *i.e.,* the terminal or omega-group; beta-oxidation then proceeds at both ends of the fatty acid chain.

overproduction t., SYN Weigert's *law.*

oxygen deprivation t. of narcosis, that narcotics inhibit oxidation, which causes the cell to be narcotized.

Pauling's t., SYN hydrate microcrystal t. of anesthesia.

permeability t. of narcosis, that the permeability of the cell membrane is decreased by narcotic concentrations of aliphatic and other central nervous system depressants.

phlogiston t., SEE phlogiston.

pithecoid t., the t. of human's descent with the ape from a common ancestor. SEE ALSO darwinian t.

place t., a t. of pitch perception which states that the perception of the pitch of a sound depends upon the level or region of the basilar membrane of the cochlea which is set into vibration by the sound waves. SEE ALSO resonance t. of hearing.

Planck's t., SYN quantum t.

polyphyletic t., SYN polyphyletism.

preformation t., archaic t. that the embryo was fully formed in miniature within a gamete at the time of conception. SEE ALSO homunculus. SYN emboitement, incasement t.

quantum t., that energy can be emitted, transmitted, and absorbed only in discrete quantities (quanta), so that atoms and subatomic particles can exist only in certain energy states. SYN Planck's t.

recapitulation t., the t. formulated by E.H. Haeckel that individuals in their embryonic development pass through stages similar in general structural plan to the stages their species passed through in its evolution; more technically phrased, the t. that ontogeny is an abbreviated recapitulation of phylogeny. SYN biogenetic law, law of biogenesis, Haeckel's law, law of recapitulation.

Reed-Frost t. of epidemics, a mathematical t. to explain how epidemics originate and continue.

reed instrument t., a no longer tenable t. stating that in human voice production the larynx functions in a manner similar to a reed musical instrument.

reentry t., that extrasystoles are due to reentry of an impulse initiated by the sinus impulse, to which the extrasystole is coupled, into the ectopic focus.

resonance t. of hearing, that the basilar membrane of the cochlea acts as a resonating structure, recording low tones from its apical turns and high tones from its basal turns. SYN Helmholtz t. of hearing.

Ribbert's t., that a neoplasm may result when a reduction in tension (exerted by adjacent tissues) leads to conditions favorable to uncontrolled growth of cell rests.

Semon-Hering t., SYN mnemic *hypothesis.*

sensorimotor t., in the developmental t. of Piaget, the postulation that during the first 18 months of life there occurs a transformation of action into thought; at first there is a gradual shift from inborn to acquired behavior, then from body-centered to object-centered activity, ultimately permitting intentional behavior and inventive thinking.

side-chain t., Ehrlich postulated that cells contained surface extensions or side chains (haptophores) that bind to the antigenic determinants of a toxin (toxophores); after a cell is stimulated, the haptophores are released into the circulation and become the antibodies. SEE ALSO receptor. SYN Ehrlich's postulate.

somatic mutation t. of cancer, that cancer is caused by a mutation or mutations in the body cells (as opposed to germ cells), especially nonlethal mutations associated with increased proliferation of the mutant cells.

Spitzer's t., an interpretation of the partitioning of the heart of mammalian embryos primarily on the basis of recapitulations of the adult structural pattern of lower forms; most frequently cited in relation to the partitioning of the truncus arteriosus to form ascending aorta and pulmonary trunk, which is achieved by the phylogenetic development of the lungs.

stringed instrument t., a no longer tenable t. stating that in human voice production the vocal cords function in a manner similar to the strings in a stringed musical instrument.

surface tension t. of narcosis, that substances which lower the surface tension of water pass more readily into the cell and cause narcosis by decreasing metabolism.

telephone t., a t. of pitch perception which states that the cochlea possesses no faculty of sound analysis, but that the frequency of the impulses transmitted over the auditory nerve fibers corresponds to the frequency of the sound vibrations, and is the sole basis for pitch discrimination; a t. no longer tenable.

thermodynamic t. of narcosis, that the interposition of narcotic molecules in nonaqueous cellular phase causes changes that interfere with facilitation of ionic exchange.

two-sympathin t., a t., now obsolete, advanced by Cannon and Rosenblueth that two different types of substances (sympathin E and I) diffuse into circulation when adrenergic nerves are stimulated, although the mediator itself is the same.

van't Hoff's t., that substances in dilute solution obey the gas laws. Cf. van't Hoff's *law.*

Warburg's t., that the development of cancer is due to irreversible damage to the respiratory mechanism of cells, leading to the selective multiplication of cells with increased glycolytic metabolism, both aerobic and anaerobic.

Wollaston's t., a t. that the semidecussation of the optic nerves at the chiasm is proved by the homonymous hemianopia seen in brain lesions.

Young-Helmholtz t. of color vision, a t. that there are three color-perceiving elements in the retina: red, green, and blue. Perception of other colors arises from the combined stimulation of these elements; deficiency or absence of any one of these elements results in inability to perceive that color and a misperception of any other color of which it forms a part. SYN Helmholtz t. of color vision.

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the·o·ther·a·py (thē-ō-thār′ă-pē). Treatment of disease by prayer or religious exercises. [G. *theos,* god, + *therapeia,* therapy]

thèque (tek). A nest or aggregation of nevocytes in the epidermis. [Fr. a small box]

ther·a·peu·sis (thār-ă-pyū′sis). **1.** SYN therapeutics. **2.** SYN therapy.

ther·a·peu·tic (thār-ă-pyū′tik). Relating to therapeutics or to the treatment, remediating, or curing of a disorder or disease. [G. *therapeutikos*]

ther·a·peu·tics (thār-ă-pyū′tiks). The practical branch of medicine concerned with the treatment of disease or disorder. SYN therapeusis (1), therapia (2). [G. *therapeutikē,* medical practice]

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theory — **the·o·ri·za·tion** \ˌthē-ə-rə-ˈzā-shən, ˌthi(-ə)r-ə-\ *n* — **the·o·riz·er** *n*

he·o·ry \ˈthē-ə-rē, ˈthi(-ə)r-ē\ *n, pl* **-ries** [LL *theoria*, fr. Gk *theōria*, fr. *theōrein*] (1592) **1** : the analysis of a set of facts in their relation to one another **2** : abstract thought : SPECULATION **3** : the general or abstract principles of a body of fact, a science, or an art ⟨music ~⟩ **4** a : a belief, policy, or procedure proposed or followed as the basis of action ⟨her method is based on the ~ that all children want to learn⟩ b : an ideal or hypothetical set of facts, principles, or circumstances — often used in the phrase *in theory* (in ~, we have always advocated freedom for all) **5** : a plausible or scientifically acceptable general principle or body of principles offered to explain phenomena ⟨wave ~ of light⟩ **6** a : a hypothesis assumed for the sake of argument or investigation b : an unproved assumption : CONJECTURE c : a body of theorems presenting a concise systematic view of a subject ⟨~ of equations⟩ *syn* see HYPOTHESIS

heory of games (1951) : GAME THEORY

heory of numbers (1811) : NUMBER THEORY

he·os·o·phist \thē-ˈä-sə-fist\ *n* (1656) **1** : an adherent of theosophy **2** *cap* : a member of a theosophical society

he·os·o·phy \-fē\ *n* [ML *theosophia*, fr. LGk, fr. Gk *the-* + *sophia* wisdom — more at SOPHY] (1650) **1** : teaching about God and the world based on mystical insight **2** *often cap* : the teachings of a modern movement originating in the U.S. in 1875 and following chiefly Buddhist and Brahmanic theories esp. of pantheistic evolution and reincarnation — **theo·soph·i·cal** \ˌthē-ə-ˈsä-fi-kəl\ *adj* — **theo·soph·i·cal·ly** \-k(ə-)lē\ *adv*

heo·to·kos \ˌthē-ə-ˈtō-(ˌ)kōs, ˌthā-, -kəs\ *n* [LGk, fr. Gk *the-* + *tokos* childbirth; akin to Gk *tiktein* to beget — more at THANE] : VIRGIN MARY

her·a·peu·sis \ˌther-ə-ˈpyü-səs\ *n* [NL, fr. Gk, treatment, fr. *therapeuein*] (ca. 1857) : THERAPEUTICS

her·a·peu·tic \-ˈpyü-tik\ *adj* [Gk *therapeutikos*, fr. *therapeuein* to attend, treat, fr. *therapōn* attendant] (1646) **1** : of or relating to the treatment of disease or disorders by remedial agents or methods ⟨a ~ rather than a diagnostic specialty⟩ **2** : providing or assisting in a cure : CURATIVE, MEDICINAL ⟨~ diets⟩ ⟨a ~ investigation of government waste⟩ — **ther·a·peu·ti·cal·ly** \-ti-k(ə-)lē\ *adv*

herapeutic index *n* (1926) : a measure of the relative desirability of a drug for the attaining of a particular medical end that is usu. expressed as the ratio of the largest dose producing no toxic symptoms to the smallest dose routinely producing cures

her·a·peu·tics \ˌther-ə-ˈpyü-tiks\ *n pl but sing or pl in constr* (1671) : a branch of medical science dealing with the application of remedies to diseases

her·a·pist \ˈther-ə-pist\ *n* (1886) : one specializing in therapy; *esp* : a person trained in methods of treatment and rehabilitation other than the use of drugs or surgery ⟨a speech ~⟩

he·rap·sid \thə-ˈrap-səd\ *n* [NL *Therapsida*, fr. *ther-* mammal (fr. Gk *thēr* wild animal) + *apsid-*, *apsis* arch, vault — more at FIERCE, APSIS] (1912) : any of an order (Therapsida) of Permian and Triassic reptiles that are considered ancestors of the mammals — **therapsid** *adj*

her·a·py \ˈther-ə-pē\ *n, pl* **-pies** [NL *therapia*, fr. Gk *therapeia*, fr. *therapeuein*] (ca. 1846) : therapeutic treatment esp. of bodily, mental, or behavioral disorder

ther·a·va·da \ˌther-ə-ˈvä-də\ *n* [Pali *theravāda*, lit., doctrine of the elders] (1882) : a conservative branch of Buddhism comprising sects chiefly in Sri Lanka, Myanmar, Thailand, Laos, and Cambodia and adhering to the original Pali scriptures alone and to the nontheistic ideal of nirvana for a limited select number — compare MAHAYANA

there \ˈthar, ˈther\ *adv* [ME, fr. OE *thēr*; akin to OHG *dār* there, OE *thæt* that] (bef. 12c) **1** : in or at that place ⟨stand over ~⟩ — often used interjectionally **2** : to or into that place : THITHER ⟨went ~ after church⟩ **3** : at that point or stage ⟨stop right ~ before you say something you'll regret⟩ **4** : in that matter, respect, or relation ⟨~ is where I disagree with you⟩ **5** — used interjectionally to express satisfaction, approval, encouragement or sympathy, or defiance ⟨~, it's finished⟩

there \ˈthar, ˈther, *T is also* thər\ *pron* (bef. 12c) **1** — used as a function word to introduce a sentence or clause ⟨~ shall come a time⟩ **2** — used as an indefinite substitute for a name ⟨hi ~⟩

there *same as* ˈ\ *n* (1588) **1** : that place or position ⟨there is no here and no ~ . . . in pure space — James Ward⟩ **2** : that point ⟨you take it from ~⟩

there *same as* ˈ\ *adj* (1590) **1** — used for emphasis esp. after a demonstrative pronoun or a noun modified by a demonstrative adjective ⟨those men ~ can tell you⟩ **2** *nonstand* — used for emphasis after a demonstrative adjective but before the noun modified ⟨I bet I cussed that ~ blamed mule five hundred times —Elizabeth M. Roberts⟩ **3** : capable of being relied on for support or aid ⟨she is always ~ for him⟩ **4** : fully conscious, rational, or aware ⟨not all ~⟩

here·abouts *also* **there·about** \ˌthar-ə-ˈbau̇t(s), ˈthar-ə-ˌ, ˌther-ə-ˈbau̇t(s), ˈther-ə-\ *adv* (bef. 12c) **1** : near that place or time **2** : near that number, degree, or quantity ⟨a boy of 18 or ~⟩

here·af·ter \ˌthə-ˈraf-tər, ˌthē-\ *adv* (bef. 12c) **1** : after that **2** *archaic* : according to that : ACCORDINGLY

here·at \-ˈrat\ *adv* (bef. 12c) **1** : at that place **2** : at that occurrence

here·by \ˌthar-ˈbī, ˌther-, ˈthar-ˌ, ˈther-\ *adv* (bef. 12c) **1** : by that : by that means ⟨~ lost her chance to win⟩ **2** : connected with or with reference to that ⟨~ hangs a tale —Shak.⟩

here·for \ˈthar-ˌfȯr, ˌther-\ *adv* (12c) : for or in return for that ⟨ordered a change and gave his reasons ~⟩

here·fore \ˈthar-ˌfōr, ˈther-, -ˌfȯr\ *adv* (14c) **1** a : for that reason : CONSEQUENTLY b : because of that c : on that ground **2** : to that end

here·from \ˌthar-ˈfrəm, ˌther-, -ˈfräm\ *adv* (13c) : from that or it

here·in \ˌthə-ˈrin, ˌthē-\ *adv* (bef. 12c) **1** : in or into that place, time, or thing **2** : in that particular or respect ⟨~ lies the problem⟩

here·in·af·ter \ˌthar-in-ˈaf-tər, ˌther-\ *adv* (1818) : in the following part of that matter (as writing, document, or speech)

there·of \ˌthə-ˈrəv, -ˈräv, ˌthē-\ *adv* (bef. 12c) **1** : of that or it **2** : from that cause or particular : THEREFROM

there·on \-ˈrȯn, -ˈrän\ *adv* (bef. 12c) **1** : on that ⟨a text with a commentary ~⟩ **2** *archaic* : THEREUPON

there·to \ˌthar-ˈtü, ˌther-\ *adv* (bef. 12c) : to that ⟨a text and the notes ~⟩

there·to·fore \ˈthar-tə-ˌfȯr, ˈther-, -ˌfȯr, ˌthar-tə-ˈ, ˌther-\ *adv* (14c) : up to that time ⟨a ~ unknown author⟩

there·un·der \ˌthə-ˈrən-dər, ˌthē-\ *adv* (bef. 12c) : under that

there·un·to \-ˈrən-(ˌ)tü, ˌthar-ən-ˈtü, ˌther-\ *adv* (14c) *archaic* : THERETO

there·up·on \ˈthar-ə-ˌpȯn, ˈther-, -ˌpän, ˌthar-ə-ˈ, ˌther-\ *adv* (13c) **1** : on that matter **2** : THEREFORE **3** : immediately after that

there·with \ˌthar-ˈwith, ˌther-, -ˈwith\ *adv* (bef. 12c) **1** : with that **2** *archaic* : THEREUPON, FORTHWITH

there·with·al \ˈthar-wi-ˌthȯl, ˈther-, -ˌthȯl\ *adv* (14c) **1** *archaic* : BESIDES **2** : THEREWITH

the·ri·ac \ˈthir-ē-ˌak\ *n* [NL *theriaca*] (1568) **1** : THERIACA **2** : CURE-ALL

the·ri·a·ca \thi-ˈri-ə-kə\ *n* [NL, fr. L, antidote against poison — more at TREACLE] (1562) : a mixture of many drugs and honey formerly held to be an antidote to poison — **the·ri·a·cal** \-kəl\ *adj*

the·rio·mor·phic \ˌthir-ē-ō-ˈmȯr-fik\ *adj* [Gk *thēriomorphos*, fr. *thērion* beast + *morphē* form — more at TREACLE] (1882) : having an animal form ⟨~ gods⟩

therm \ˈthərm\ *n* [Gk *thermē* heat, fr. *thermos* hot; akin to L *formus* warm, Skt *gharma* heat] (1888) : a unit used to measure quantity of heat that equals 100,000 British thermal units

therm- *or* **thermo-** *comb form* [Gk, fr. *thermē*] **1** : heat ⟨*thermo*stat⟩ **2** : thermoelectric ⟨*thermo*pile⟩

-therm *n comb form* [Gk *thermē* heat] : animal having a (specified) body temperature ⟨ecto*therm*⟩

¹ther·mal \ˈthər-məl\ *adj* [Gk *thermē*] (1756) **1** [L *thermae* public baths, fr. Gk *thermai*, pl. of *thermē*] : of, relating to, or marked by the presence of hot springs ⟨~ waters⟩ **2** a : of, relating to, or caused by heat ⟨~ stress⟩ ⟨~ insulation⟩ b : being or involving a state of matter dependent upon temperature ⟨~ conductivity⟩ ⟨~ agitation of molecular structure⟩ **3** : designed (as with insulating air spaces) to prevent the dissipation of body heat ⟨~ underwear⟩ **4** : having energies of the order of those due to thermal agitation ⟨~ neutrons⟩ — **ther·mal·ly** \-mə-lē\ *adv*

²thermal *n* (1933) : a rising body of warm air

ther·mal·ize \ˈthər-mə-ˌlīz\ *vt* **-ized; -iz·ing** (1948) : to change the effective speed of (a particle) to a thermal value ⟨~ a neutron⟩ — **ther·mal·i·za·tion** \ˌthər-mə-lə-ˈzā-shən\ *n*

thermal pollution *n* (1966) : the discharge of heated liquid (as wastewater from a factory) into natural waters at a temperature harmful to the environment

thermal printer *n* (1966) : a dot matrix printer (as for a computer) in which heat is applied to the pins of the matrix to form dots on usu. heat-sensitive paper

ther·mic \ˈthər-mik\ *adj* (1842) : THERMAL 2 ⟨~ energy⟩ — **ther·mi·cal·ly** \-mi-k(ə-)lē\ *adv*

therm·ion·ic \ˌthər-(ˌ)mī-ˈä-nik\ *adj* [*thermion* charged particle from an incandescent source, fr. *therm-* + *ion*] (1909) : relating to, using, or being the emission of charged particles (as electrons) by an incandescent material

therm·ion·ics \ˌthər-(ˌ)mī-ˈä-niks\ *n pl but sing in constr* (1909) : physics dealing with thermionic phenomena

therm·is·tor \ˈthər-ˌmis-tər\ *n* [*thermal resistor*] (1940) : an electrical resistor making use of a semiconductor whose resistance varies sharply in a known manner with the temperature

Ther·mit \ˈthər-mət, -ˌmit\ *trademark* — used for thermite

ther·mite \ˈthər-ˌmit\ *n* [*therm-* + *¹-ite*] (1900) : a mixutre of aluminum powder and a metal oxide (as iron oxide) that when ignited evolves a great deal of heat and is used in welding and in incendiary bombs

ther·mo·chem·is·try \ˌthər-mō-ˈke-mə-strē\ *n* (1844) : a branch of chemistry that deals with the interrelation of heat with chemical reaction or physical change of state — **ther·mo·chem·i·cal** \-ˈke-mi-kəl\ *adj* — **ther·mo·chem·ist** \-ˈke-mist\ *n*

ther·mo·cline \ˈthər-mə-ˌklīn\ *n* (1898) : the region in a thermally stratified body of water which separates warmer oxygen-rich surface water from cold oxygen-poor deep water and in which temperature decreases rapidly with depth

ther·mo·cou·ple \ˈthər-mə-ˌkə-pəl\ *n* (1890) : a device for measuring temperature in which a pair of wires of dissimilar metals (as copper and iron) are joined and the free ends of the wires are connected to an instrument (as a voltmeter) that measures the difference in potential created at the junction of the two metals

ther·mo·du·ric \ˌthər-mō-ˈdu̇r-ik, -ˈdyu̇r-\ *adj* [*therm-* + L *durare* to last — more at DURING] (1927) : able to survive high temperatures; *specif* : able to survive pasteurization — used of microorganisms

ther·mo·dy·nam·ic \ˌthər-mō-dī-ˈna-mik, -də-\ *also* **ther·mo·dy·nam·i·cal** \-mi-kəl\ *adj* (1849) **1** : of or relating to thermodynamics **2** : being or relating to a system of atoms, molecules, colloidal particles, or larger bodies considered as an isolated group in the study of thermodynamic processes — **ther·mo·dy·nam·i·cal·ly** \-mi-k(ə-)lē\ *adv*

ther·mo·dy·nam·ics \-miks\ *n pl but sing or pl in constr* (1854) **1** : physics that deals with the mechanical action or relations of heat **2** : thermodynamic processes and phenomena — **ther·mo·dy·nam·i·cist** \-ˈna-mə-sist\ *n*

ther·mo·elec·tric \ˌthər-mō-i-ˈlek-trik\ *adj* (1823) : of, relating to, or dependent on phenomena that involve relations between the temperature and the electrical condition in a metal or in contacting metals